Level of Assurance Provided by Existing Guidelines, Especially ICH Q5A & Q5D

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Intent

- Both ICH Q5A (Virus Safety) & Q5D (Cell Substrates) are intended to minimize the potential for the biologically active agents to contaminate biological products, and to prevent the transmission of such agents to product recipients

ICH Q5D

- Official in 1998
- Scope:
  - (animal or microbial) cell subtrates which have cell banks used to prepare biological/ biotechnological products
  - (not intended to represent a complete description of the in process testing, lot release testing, process validation, or cGMP controls needed to prepare biological/biotechnological products necessary to control potential issues)

ICH Q5D

- Specifically covers some concerns
  - potential bacterial & fungal contaminants
  - potential mycoplasmal contaminants
  - other cells as potential contaminants
- Viral contaminants deferred to ICH Q5A

Bacterial & Fungal Contaminants

- Test MCB & WCB for presence of bioburden
  - 1% of containers but not less than 2 containers
  - Current methods of EP, JP, or USP for testing microbial limits or microbial sterility may be considered adequate
- (Note that there is no requirement to demonstrate sterility, which is beyond current cell banking technology to achieve)

Mycoplasmal Contaminants

- Test MCB & WCB for presence of mycoplasma
  - Testing a single containers is adequate
  - Current methods of EP, JP, or FDA PTC for testing for presence of mycoplasma may be considered adequate

Other Cells as Potential Contaminants

- Methods used to assess cell identity are usually considered adequate to assure absence of other organisms, but care should be taken to prevent cross contamination
- (While sensitivity of identity tests to detect non-host contamination is limited, procedural & engineering controls provide assurance of lack of other cell contaminants)

Future Considerations

- Present bioburden & mycoplasma test methods are region-specific
- If Pharmacopeiae & regulatory bodies succeed in the future to harmonize methods for testing for the presence of bioburden & mycoplasma, then the scientifically appropriate harmonized assay should be used

Other Thoughts

- For concerns about bioburden & mycoplasma contamination of biological/ biotechnological products, testing cell banks is only the beginning
  - regulatory requirement to test pre-harvest cell culture
  - some processes also look at bioburden levels at many stages of cell culture & purification
  - for bioburden, DS & DP also tested for sterility
- cGMP controls exist throughout the process
- Multiple levels of testing & protection exist to prevent product contamination, therefore the rigor of the cell bank testing need not be exhaustive

ICH Q5A

- Official in 1998
- Scope:
  - biological/biotechnological products derived from animal cell cultures initiated from characterized cell banks
  - includes purified proteins from natural, rDNA, or hybridoma sources whether cells cultured *in vitro* or *in vivo*, and rDNA derived vaccines
  - does not cover conventional vaccine or gene therapy products (but many of the principles are relevant)

ICH Q5A Approach

- Viral safety of products can only be assured by application of a virus testing program *and* assessment of virus removal and inactivation assured by the manufacturing process
- Three complimentary approaches include
  - Selecting & testing cell lines & raw materials
  - Assessing the capacity of the production process to clear infectious viruses
  - Testing product at appropriate stage of production

ICH Q5A Approach to Testing

- Tests recommended were based on the reliable & sensitive tests of the 1990s
  - Manufacturers were encouraged to be flexible, and to base the testing plans on the details of the process, the types of viruses likely to be encountered, and the most sensitive point of sampling
  - Manufactures were encouraged to be open to newer tests which would be sensitive & reliable

ICH Q5A Approach to Clearance

- Clearance studies would serve as a complimentary approach to testing
  - Together with testing and routine procedural & engineering controls, clearance studies on well-designed processes would assure freedom from product contamination by infectious viruses
- Clearance approaches, like testing approaches, should be tailored to the process & product, and integrated

Other Thoughts

- For concerns about virus contamination of biological/ biotechnological products, testing cell banks is only the beginning
  - regulatory requirement to test pre-harvest cell culture by sensitive *in vitro* tests
  - testing raw materials of animal origin before use is also important
  - some processes also look at levels of contamination of cell culture just before harvest & purification by a rapid PCR test
- cGMP controls (procedural & engineering) exist throughout the process
- Multiple levels of testing & protection exist to prevent product contamination, therefore the rigor of the cell bank testing or preharvest bulk testing need not be exhaustive

How Effective Are ICH Q5A & D?

- The principles embodied in these documents are built on 100 years of history of contamination of processes & products, and infected recipients
- The use of these procedures has detected contamination in a few facilities before the products were released for distribution
- These programs have allowed tens of millions of product recipients to receive safe and effective medicines without evidence of associated infection during the past 20 years

Summary

- The strength of the ICH Q5A & Q5D recommendations lies not in the rigor of individual tests, but in the integration of a prudent testing program at several stages with effective procedural & engineering cGMP controls, and clearance steps
- While anything can be improved, there is no clear evidence of need to change at this time for products of the same or similar technology